REMARKS

Claims 1-10 are currently pending. Pending claims 1-10 were rejected in the most recent Office Action. .

The rejection under 35 U.S.C. 112, first paragraph

The Office has rejected claims 1-6 and 9-10 as purportedly not enabled. Respectfully, the Applicants defer to previous comments provided with respect to this rejection, and, in addition, provide the following discussion.

The current rejection asserts that the Applicants have not:

- provided sufficient guidance for electing suitable photosensitizers for use in the claimed invention;
- presented working examples to show how all of the claimed photosensitizers may be used in the present invention; and
- adequately defined porphyrin derivatives or photosensitizers

The rejection also asserts that due to the unpredictability in the entire art of pharmaceuticals, one of skill in the art would expect different photosensitizer compounds to yield a different result in restenosis or intimal hyperplasia. Applicants respectfully traverse.

As an initial matter, Applicants would like to note that the subject matter of claim 6 is directed to porphyrin derivatives. All porphyrin derivatives contain analogous structures and have similar activity in terms of photosensitizing activity. Further, a working example is provided of a specific porphyrin derivative in Example 1. Despite all of these reasons for the subject matter of claim 6 to be enabled by the application as filed for practice by the skilled artisan, the rejection provides no objective reason why the subject matter of claim 6 would require undue experimentation for its practice. Once again, Applicants would like to would like to point out that MPEP 2164.04 sets forth the standard of *In re Marzocchi* (169 USPQ 367 (CCPA 1971)) where claims must be taken as being enabled unless there is reason to doubt the

objective truth of the statements of an application in support of enablement. Applicants respectfully submit that no adequate reasons have been provided in the instant rejection with respect to the subject matter of claim 6.

Similarly, no objective reasons for doubting the enablement for the subject matter of claim 1 has been provided. Applicants respectfully point out that it not necessary to exhaustively determine which photosensitizer works prior to use in the present invention. There is simply no requirement for absolute predictability in the standard for objective enablement in U.S. law. Moreover, and contrary to the Examiner's first assertion listed above, there is guidance for the skilled person to make and use the claimed invention. The rejection has provided no reason why a skilled person would not be able to administer any photosensitizer in a method as encompassed by the claims and determine the appropriate conditions for its use. To the contrary, the Examiner has recognized that optimization of conditions is routine in the art (see rejection under 35 USC 103(a)).

Despite differences between different photosensitizer compounds, there is a common feature of photosensitizing activity that is common to all photosensitizers which makes all of them reasonable for the practice of the invention as claimed. The Office has cited no references refuting or rebutting this assertion. The common feature is the simple requirement that they be photosensitizers (or, stated differently, be capable of photoactivation). Photoactivation is a requirement for the claims as presented, and would lead a skilled artisan to expect that any photosensitizer would be suitable for the practice of the invention. The Examiner has also asserted that "[t]he pharmaceutical art is unpredictable." Without commenting on the validity of this assertion, Applicants respectfully point out that this appears to be too broad a statement to be meaningful in the instant application, where the invention is not directed to the pharmaceutical art as a whole, but rather directed to the narrower field of photosensitizers. Without objective evidence, it is not understood how unpredictability in the entire "pharmaceutical art" affects the present claims, where predictability is present in the common photosensitizing functionality.

According to the invention as currently claimed, the use of a photosensitizer requires its administration at a certain dosage followed by irradiation of a certain wavelength and energy to activate it. These features are clearly disclosed in the specification and also known in the art. Thus the actual amount of experimentation to determine the conditions for the use of any photosensitizer only requires routine (or repetitive) practice of a limited number of parameters rather than any experimentation and design for *de novo* discovery. Such repetitive experimentation is completely within the limits permitted by the standards for objective enablement. As provided by the Federal circuit, experimentation may not be considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation -- time and difficulty are not determinative of undue experimentation if the experimentation is routine. *See PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); see also *Wands*, 8 USPQ2d 1400, 1403-07; MPEP § 2164.06.

The Federal Circuit in *Wands* held that experimentation involving the screening of numerous hybridomas, inherently involving the screening of inoperative embodiments, was not undue. *See Wands*, 8 USPQ2d at 1407 (determining that "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for desired characteristics" did not involve undue experimentation). The Office has cited no objective reason as to why the level of experimentation required for the practice of the claimed invention would be other than routine for a person skilled in the art. This is especially difficult to comprehend in light of the "routine to optimize" statements as part of the rejection under 35 USC 103(a).

As to specific directions for use in treatment, optimization of dosage and administration are routine matters of routine experimentation once the active ingredient is identified, as it has been here. *See e.g.*, specification at page 12, line 27 to page 17, line 15 and the Examples.

With regard to the second assertion regarding working examples, Applicants would initially like to direct the Office's attention to the Examples section where working examples are provided. Principles from these examples are equally applicable to all photosensitizers. In general, if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. § 112 is satisfied. *See In re Brana,* 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). The requisite showing of the enablement of a claimed therapeutic composition is that information provided in the specification must "be reasonably indicative of the desired pharmacological response." *Fujikawa v. Wattansin*, 39 USPQ2d 1895 (Fed. Cir. 1996) (citations omitted). As held by the Federal Circuit, information provided need not "absolutely prove that a compound is pharmacologically active." *Id.* "In other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior." *Id.* (emphasis added). Photosensitizers selected based on the criteria provided certainly have a reasonable probability of exerting the required pharmacological effect. Therefore, if one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. Section 112. As acknowledged by the Office, "[o]ptimization of result effect parameters . . . is obvious as being within the skill of an artisan." (*See* Office Action page 7).

The instant rejection has provided no reason why the skilled artisan would not view the claims as complying with the above standards.

With regard to the third assertion, Applicants respectfully assert that these terms are indeed broad but understood by those skilled in the art. Further definition beyond that provided in the specification as applying to the present invention is not required for practicing the presently claimed invention. The present invention involves the use of low-dose photodynamic

therapy (PDT) to prevent, treat, inhibit or reduce restenosis and associated intimal hyperplasia in blood vessels. As provided in the specification, PDT involves the use of photosensitizers which are further defined as compounds that absorb a specific wavelength radiation, become activated and produce a toxic agent. *See* specification, e.g., at page 2, lines 7-8. The invention as currently claimed utilizes photosensitizers which fill this criteria and prevent, treat, inhibit, or reduce restenosis or intimal hyperplasia without depleting all endothelial and smooth muscle cells. Examples of acceptable photosensitizers for the present invention based on this criteria are provided throughout the present disclosure. As provided above, the selection of appropriate photosensitizers involves no more than routine experimentation.

For the above reasons, Applicants respectfully submit that no prima facie case of a lack of enablement has been presented, and the rejection may be properly withdrawn.

The rejection under 35 U.S.C. 112, second paragraph

The Office has rejected claims 1-10 under 35 U.S.C. 112, second paragraph, as purportedly indefinite. The Office has asserted that method steps are missing regarding preventing or treating intimal hyperplasia or restenosis without the depletion of smooth muscle cells. The basis for this assertion apparently lies in the Examiner's observation that "the prior art teaches that the result of the photodynamic therapy will deplete all cells." (Office Action page 6).

Respectfully, Applicants submit that the depletion of smooth muscle cells is avoided in the present invention through the practice of the claimed methods. The invention as currently claimed is limited to a method whereby the depletion of all endothelial and smooth muscle cells is avoided. All steps required for this result are provided in the claims including the use of low dose irradiation and a working examples are presented in the specification. If depletion of all endothelial and smooth muscle cells results from a purported practice of the claimed invention, then it is obvious that it was not within the scope of the invention as claimed.

Further, it is not understood how the claims are indefinite based on the bare assertion that the purported "prior art" has failed to achieve this result. "[S]tatements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained." *In re Cortright*, 49 USPQ2d 1464, 1466 (Fed. Cir. 1999). Therefore, the basis for this rejection apparently lies in the unsupported assertion which weighs in favor of the patentability of the present invention. In other words, if the practice of all purported "prior art" results in the depletion of all cells, then the current claims are directed to an invention beyond the "prior art".

The rejection under 35 U.S.C. 103(a)

The Office has again rejected claims 1-10 as allegedly unpatentable over Vincent et al. in view of Adili et al. Applicants have carefully reviewed the statement of this rejection as well as the contents of the cited references and traverse as follows.

As an initial matter, Applicants note that the instant rejection is based upon combining a reference (Vincent et al.) that teaches the use of photosensitizers without the use of photoactivation and a second reference (Adili et al.) that teaches the use of photosensitizers with photoactivation. It is not understood why or how an artisan of ordinary skill with knowledge of Vincent et al. would modify it for practice with the use of irradiation. Vincent expressly states that the method disclosed therein is to be performed "without irradiation by light absorbed by the green porphyrin administered." (Vincent et al. column 3, lines 42-44). While PDT is discussed in the background art of Vincent et al., however, the object of Vincent is clearly to avoid the use of irradiation of administered photosensitizers. Thus, this reference appears to teach away from the present invention, and thus cannot render the present claims obvious, in that the present invention uses irradiation. As provided recently by the Federal Circuit, "[r]eferences that teach away cannot serve to create a prima facie case of obviousness." *McGinley v. Franklin Sports,*

Inc., 60 USPQ2d 1001, 1010 (Fed. Cir. 2001) (citing *In re Gurley*, 31 USPQ2d 1131, 1132 (Fed Cir. 1994)).

Further, there exists no motivation to combine Vincent et al. with Adili et al. Adili et al. teaches the use of 25 μg/ml of BPD-MA with a high light dosage of 100 J/cm^2. (*See* Adili et al. at page 265). The non-obvious nature of the lower PDT dosages of the instant claims is supported by a later publication by Adili et al. as noted in the instant specification on page 5, lines 1-11, where a PDT at 0.5 μg/ml of BPD-MA with a light dosage of 50 J/cm^2 was already observed to have little effect on reducing IH. Why then would an artisan of ordinary skill look to light dosages as low as 0.25 to 3 J/cm^2 as used in the instant examples? The instant rejection thus appears to be based upon the impermissible "obvious to try" lower PDT dosages standard.

Additionally, Adili et al. teach that their conditions result in an "acellular media even 21 days after PDT" (*See* Adili et al. page 272, last sentence of first full paragraph). This is in contrast to the assertion that column 11, lines 16-19, of Vincent discloses conditions that do not deplete all cells. The rejection provides no explanation of how an artisan was to choose between the two possibilities to arrive at the claimed invention without reliance upon impermissible hindsight based on the instant application?

As provided by the Federal Circuit, motivation to combine references must be present otherwise a combination thereof is not considered obvious. Requisite motivation requires a desirable combination of references rather than a combination of what is feasible. *See Winner Int'l Royalty Corp. v. Ching-Rong Wang*, 53 USPQ2d 1580, 1587 (Fed. Cir. 1990). "Although a reference need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability, in whatever form, must nevertheless be 'clear and particular.'" *Id.* at 1586-87 (quoting *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citations omitted). Based on the foregoing and the inadequate statements in the rejection, there exists no suggestion or motivation to combine, nor any showing of combinability, of Vincent et al. with Adili et al. to arrive at the present invention.

With respect to the Office's assertion that no clear an convincing unexpected results has been presented, Applicants note that evidence of unexpected results may be considered when a *prima facie* showing of obviousness has been presented. The Applicants respectfully submit that based no such showing has been provided by the Office.

Lastly, on page 9 of the current Office Action, the Examiner appears to have based part of the obviousness rejection on an alleged non-enablement of how to practice the claimed invention (of not depleting all cells) in light of the art teaching total cell depletion. It is not understood by Applicants how this alleged lack of enablement supports an assertion of obviousness. If the claims encompass something beyond the art, the art does not apply even if the claims are simultaneously asserted as being non-enabled for their scope.

Moreover, this portion of the rejection appears to be contradictory to the last sentence of the rejection concerning how the optimization of PDT to not deplete cells is "within the purview of the skilled artisan." While Applicants generally agree with this assertion, why would the claims not be enabled for the skilled artisan?

This also appears contradictory to the assertion of indefiniteness as discussed above. If conditions for not depleting cells are within the skill in the art, how can the claims be indefinite for the not reciting those conditions?

Applicants thus respectfully submit that the references, alone or in combination, do not teach or suggest the invention as claimed, and that no prima facie case of obviousness has been presented. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants believe that the claims are in condition for allowance and urge passage of the application to issue. The Examiner is invited to

contact Applicants' agent at the number listed below if it would be helpful in any way to resolve any remaining issues.

In the event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 273012012200. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By: _____

Kawai Lau
Registration No. 44,461

Morrison & Foerster LLP
3811 Valley Centre Drive - Suite 500
San Diego, CA 92130-2332
Telephone: (858) 720-5178
Facsimile: (858) 720-5125